UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,370	04/28/2006	Daniel Lucius Vasella	4-33452-US-PCT	4959

1095 7590 03/27/2008

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
POLANSKY, GREGG	
ART UNIT	**PAPER NUMBER**
1611	

MAIL DATE	DELIVERY MODE
03/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,370	VASELLA, DANIEL LUCIUS	
	Examiner	Art Unit	
	GREGG POLANSKY	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/2008 & 1/28/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicant's preliminary amendments, filed 4/28/2006, amending Claim 4 and adding Claims 8 and 9, are acknowledged.

2. Applicant's Information Disclosure Statements, filed 1/25/2008 and 1/28/2008, are acknowledged and have been reviewed to the extent each is a proper citation on a U.S. Patent.

3. Applicant's election of the species valsartan, hydrochlorothiazide and hypertension in the reply filed on 1/15/2008 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The Restriction Requirement is thus deemed to be proper and is made Final.

4. Claims 1-9 are pending and are presently under consideration.

5. Claims 1-6, 8 and 9 are drawn to pharmaceutical combinations and compositions.

Specification

6. The disclosure is objected to for the following informality: "triamterene" is incorrectly spelled.

Appropriate correction is required.

Claim Objections

7. Claims 1, 5 and 7 are objected to for the following informalities: "triamterene" is incorrectly spelled.

8. Claim 3 is objected to for the following informality: Hydrochloride is missing the "e". Appropriate correction is required.

9. Claims 8 and 9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of Claims 2 and 3, respectively. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form. Claims 8 and 9 are drawn to pharmaceutical compositions comprising a combination according to Claims 2 and 3, respectively. Claims 2 and 3 are drawn to a combination of three agents. A composition is a product of mixing or combining various elements or ingredients. Claims 2 and 3 are drawn to a combination of three agents and is therefore a composition of the three agents.

Claim Rejections - 35 USC § 112 and 35 USC §101

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claims 1- 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding Claim 1, the phrase "such as" renders the claim indefinite because it is unclear whether or not claim limitations are intended. See MPEP § 2173.05(d).

Claims 5-7 contain parenthetical subject matter that renders the claims indefinite because it is not clear whether “antiproliferative effect of the combination” in parentheses is a limitation or an option remodeling following hypertension.

12. Claim 6 provides for the use of a combination for the manufacture of a medicament, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 6 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention. The claims are directed to the prevention, delay of progression or treatment of a plethora of diseases and conditions, including hypertension, congestive heart failure, atherosclerosis, obesity, hypothyroidism, diabetes mellitus type 2, endothelial dysfunction, hyperlipidemia and glaucoma, comprising administering an AT1-receptor antagonist, the diuretic amiloride or triamterene, and an additional diuretic. The target population is either not recited or is any warm-blooded animal (e.g., this could include, besides man, birds, porpoises, bats, and kangaroos). The Specification does not reasonably provide enablement for the methods of prevention within the full scope of the claimed compounds. To be enabling, the Specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547,

the court recited eight factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are: 1) the quantity of experimentation necessary 2) the amount of direction or guidance provided 3) the presence or absence of working examples 4) the nature of the invention 5) the state of the art 6) the relative skill of those in the art 7) the predictability of the art and 8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The invention is drawn to the prevention, delay of progression, or treatment of a plethora of diseases and conditions, including hypertension, congestive heart failure, atherosclerosis, obesity, hypothyroidism, diabetes mellitus type 2, endothelial dysfunction, hyperlipidemia and glaucoma, comprising administering an AT_1-receptor antagonist, the diuretic amiloride or triamterene, and an additional diuretic.

The group of the diseases/conditions recited by the instant claims has diverse etiologies. Indeed, each individual disease/condition may itself have different etiologies. For example, when limiting the scope of the claims to preventing diabetic retinopathy, the prior art teaches that diabetic retinopathy is the inevitable microvascular

complication in the retina from diabetes mellitus and there is still no effective cure-all therapy for diabetes mellitus. See Ting et al., "Basic and clinical aspects of gene therapy for retinopathy induced by diabetes", Curr Gene Ther., 2006, Apr; 6(2):193-214; also see information on http://www.faqs.org/health/Sick-V2/Diabetes-Mellitus.html. Thus, it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "preventive" effect.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. with expertise in the area of internal medicine.

However, that factor is outweighed by the diversity of the diseases/conditions recited by the claims and their diverse and incompletely understood etiologies. In cases involving unpredictable factors, such as the instant claims drawn to physiological activity, the scope of enablement varies inversely with the degree of unpredictability of the factors involved. Also, one skilled in the chemical or biological arts cannot always reasonably predict how different chemical compounds might behave under varying circumstances. See *Ex parte Sudilovsky*, 21 USPQ2d 1701.

The amount of direction or guidance provided and the presence or absence of working examples

The guidance or direction provided by the instant Specification is limited to the statement or page 5, “[t]he person skilled in the pertinent art is fully enabled to select a relevant and standard animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects” of the pharmaceutical

combination/composition, and some examples of such models, with prophetic results. The Specification is clearly not predictive for prevention of the diseases or conditions claimed. The skilled artisan would not reasonably expect that the claimed pharmaceutical combination composition could be used to prevent one, much less all, diseases/conditions.

There are no working examples drawn to a prevention modality in which the claimed pharmaceutical combination composition is shown to be clinically effective for prevention of the recited diseases/conditions.

The term "prevention" is an absolute definition that means to stop from occurring and thus requires a higher standard for enablement than does "therapeutic" or "treat". It is well established in the medical arts that the vast majority of diseases suffered by mankind cannot be totally prevented with current therapies.

The quantity of experimentation necessary

Applicants have failed to provide guidance as to the efficacy of any of the vast number of possible AT_1-receptor antagonist/multi-diuretic combinations for preventing the plethora of diseases/conditions. The skilled artisan would expect the interaction of particular compounds in the prevention of the diseases/conditions to be very specific and highly unpredictable absent a clear understanding of the structural, biochemical and physiological basis for the combination of agents. The instant specification sets forth no such understanding. No direction is provided to distinguish therapy among the various compounds that are encompassed in the Claims (i.e., AT_1-receptor antagonists, amiloride or triamterene, and at least one other diuretic). Absent reasonable *a priori*

expectations of success for using a particular combination of AT_1-receptor antagonist, amiloride or triamterene, and an additional diuretic, one skilled in the art would have to test extensively many combinations to discover which combination in particular exhibits an effect in treating or preventing each of the diseases/conditions. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The Specification provides inadequate guidance to do otherwise.

Prevention entails the complete and absolute inhibition of the onset of each of the diseases/conditions recited and any manifestation of the disease entirely. Due to the known unpredictability of the art, and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the recited diseases/conditions could be prevented following the administration of any combination of the potential pharmaceutical combinations/compositions. Accordingly, the instant claims do not comply with the enablement requirements of 35 U.S.C. 112, first paragraph, since to practice the claimed invention would require a person of ordinary skill in the art to engage in undue experimentation with no assurance of success.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wellington et al. (Drugs, Vol. 62(13), 2002), in view of MODURETIC® Product Description (Merck & Co., Inc., 2002).

Wellington et al. teach the combination of the AT_1-receptor antagonist valsartan and the diuretic hydrochlorothiazide and its use in the treatment of hypertension. The reference teaches the combination of the two drugs, each of which is used individually in the treatment of hypertension, is significantly more effective than either drug alone. See page 1984, Abstract.

The Merck reference teaches MODURETIC® is a pharmaceutical product consisting of amiloride hydrochloride and hydrochlorothiazide. The reference teaches "MODURETIC® provides diuretic and antihypertensive activity (principally due to the hydrochlorothiazide component) while acting through the amiloride component to prevent the excessive potassium loss that may occur in patients receiving a thiazide diuretic". See page 1, Description, 1st paragraph, and Clinical Pharmacology, 1st paragraph. The reference teaches MODURETIC® is indicated "in those patients with hypertension or with congestive heart failure who develop hypokalemia when thiazides or other kaliuretic diuretics are used alone, or in whom maintenance of normal serum potassium levels is considered to be clinically important). Furthermore, the reference teaches MODURETIC® may be used alone or as an adjunct to other antihypertensive drugs. See page 2, Indications and Usage.

With regard to instant Claims 5 and 6, intended use confers no patentable weight to composition claims. *In re Hack*, 114 USPQ 161.

It would have been obvious to one of ordinary skill in the art (e.g., a medical internist) at the time of the invention to combine the above teachings to produce an effective treatment for hypertension or congestive heart failure, especially in subjects susceptible to hypokalemia or in whom maintenance of normal serum potassium levels is clinically important. Said artisan would have been motivated to do so to improve upon what was known in the art for the treatment of hypertension or congestive heart failure.

It is generally *prima facie* obvious to use in combination two or more agents that have previously been used separately for the same purpose. *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-6, 8-10 of copending Application No. 10/416039. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims encompass all of the components of the instant claims, and the open language of the instant claims allows for the inclusion of additional agents.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

18. Claims 1-9 are rejected.

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GREGG POLANSKY whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1611

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614